

Attorney Docket No. 029318/0961

We claim:

1. A stable nanoparticulate liquid dosage composition comprising:
- (a) particles of at least one active agent having an effective average particle  
5 size of less than about 2000 nm;
- (b) at least one surface stabilizer; and
- (c) at least one osmotically active crystal growth inhibitor.

2. The composition of claim 1, wherein the active agent particles form  
10 crystals upon storage or heating in the absence of the crystal growth inhibitor.

3. The composition of claim 1, wherein the osmotically active crystal growth  
inhibitor is at least partially water-soluble and does not solubilize the nanoparticulate  
active agent.

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4. The composition of claim 3, wherein the osmotically active crystal growth  
inhibitor is selected from the group consisting of glycerol, propylene glycol, mannitol,  
sucrose, glucose, fructose, mannose, lactose, xylitol, sorbitol, trehalose, a polysaccharide,  
a mono-polysaccharide, a di-polysaccharides, a sugars, a sugar alcohol, sodium chloride,  
20 potassium chloride, magnesium chloride, and an ionic salt.

5. The composition of claim 4, wherein the crystal growth inhibitor is  
glycerol.

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6. The composition of claim 4, where the crystal growth inhibitor is mannitol.

7. The composition of claim 4, where the crystal growth inhibitor is sodium  
chloride.

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8. The composition of claim 1, wherein the amount of the crystal growth inhibitor present in the liquid dosage form ranges from about 0.1% to about 95% concentration, by weight.

5 9. The composition of claim 1, wherein the amount of the crystal growth inhibitor present in the liquid dosage form ranges from about 0.5% to about 90% concentration, by weight.

10 10. The composition of claim 1, wherein the effective average particle size of the nanoparticulate active agent particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

20 11. The composition of claim 1 or 10, wherein at least about 70%, at least about 90%, or at least about 95% of the active agent particles have a particle size less than the effective average particle size.

25 12. The composition of claim 1, wherein the amount of the active agent per ml is equal to or greater than the amount of the active agent per ml of a standard conventional non-nanoparticulate liquid dosage composition of the same active agent.

30 13. The composition of claim 1, wherein the liquid media of the liquid dosage composition is selected from the group consisting of water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, and glycol.

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14. The composition of claim 1, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

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15. The composition of claim 1 formulated into a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

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16. The composition of claim 1, wherein the at least one active agent is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the active agent and at least one surface stabilizer, not including other excipients.

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17. The composition of claim 1, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the active agent and at least one surface stabilizer, not including other excipients.

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18. The composition of claim 1, wherein the ratio of active agent to a polymeric surface modifier is selected from the group consisting of from about 20:1 to about 1:10, from about 10:1 to about 1:5, and from about 5:1 to about 1:1, by weight.

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19. The composition of claim 1, comprising at least two surface stabilizers.

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20. The composition of claim 19, wherein the ratio of active agent to the second surface stabilizer is selected from the group consisting of from about 500:1 to about 5:1, from about 350:1 to about 10:1, and from about 100:1 to about 20:1, by weight.

5 21. The composition of claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

22. The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a  
10 polymeric surface stabilizer, a nonionic surface stabilizer, and a zwitterionic surface stabilizer.

23. The composition of claim 22, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein,  
15 phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates,  
20 colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde,  
25 poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl  $\beta$ -D-glucopyranoside; n-decyl  $\beta$ -D-maltopyranoside; n-dodecyl  $\beta$ -D-glucopyranoside; n-dodecyl  $\beta$ -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-  
30  $\beta$ -D-glucopyranoside; n-heptyl  $\beta$ -D-thioglucoside; n-hexyl  $\beta$ -D-glucopyranoside;

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nonanoyl-N-methylglucamide; n-nonyl  $\beta$ -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- $\beta$ -D-glucopyranoside; octyl  $\beta$ -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, and random copolymers of vinyl acetate and vinyl pyrrolidone.

5

24. The composition of claim 22, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, a phospholipid, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, 10 hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, 15 decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C<sub>12-15</sub>dimethyl hydroxyethyl ammonium chloride, C<sub>12-15</sub>dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl 20 ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)<sub>4</sub> ammonium chloride, lauryl dimethyl (ethenoxy)<sub>4</sub> ammonium bromide, N-alkyl (C<sub>12-18</sub>)dimethylbenzyl ammonium chloride, N-alkyl (C<sub>14-18</sub>)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C<sub>12-14</sub>) dimethyl 1-naphthylmethyl 25 ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C<sub>12-14</sub>) dimethyl 1- 30 naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl

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benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C<sub>12</sub> trimethyl ammonium bromides, C<sub>15</sub> trimethyl ammonium bromides, C<sub>17</sub> trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyl dimethyl ammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearylalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™, ALKAQUAT™, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

25. The composition of any of claims 22 or 24, wherein the composition is bioadhesive.

26. The composition of claim 1, wherein the active agent is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, and mixtures thereof.

27. The composition of claim 1, wherein the one or more active agents have a solubility in water selected from the group consisting of less than about 30 mg/ml, less than about 20 mg/ml, less than about 10 mg/ml, and less than about 1 mg/ml, under ambient conditions.

28. The composition of claim 1 wherein the active agent comprises anti-inflammatory and analgesic properties.

29. The composition of claim 1, wherein the at least one active agent is selected from the group consisting of COX-2 inhibitors, anticancer agents, NSAIDS,

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proteins, peptides, nutraceuticals, anti-obesity agents, corticosteroids, elastase inhibitors, analgesics, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, xanthines, acne medication, alpha-hydroxy formulations, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, and respiratory illness therapies associated with acquired immune deficiency syndrome.

30. The composition of claim 29, wherein the nutraceutical is selected from the group consisting of dietary supplements, vitamins, minerals, herbs, healing foods that have medical or pharmaceutical effects on the body, folic acid, fatty acids, fruit and vegetable extracts, vitamin supplements, mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish and marine animal oils, and probiotics.

31. The composition of claim 1, wherein the active agent is selected from the group consisting of acyclovir, alprazolam, altretamine, amiloride, amiodarone, benzotropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin, cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine,

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cyproheptadine, delavirdine, desmopressin, diltiazem, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine, felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole, loratadine, loxapine, mebendazole, mercaptopurine, milrinone lactate, minocycline, mitoxantrone, nelfinavir mesylate, nimodipine, 5 norfloxacin, olanzapine, omeprazole, penciclovir, pimozide, tacolimus, quazepam, raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, sertraline, sildenafil, acetyl-sulfisoxazole, temazepam, thiabendazole, thioguanine, trandolapril, triamterene, trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenolate, atovaquone, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, 10 thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, and acetylsalicylate.

32. The composition of claim 1, wherein the viscosity of the composition, at a shear rate of 0.1 (1/s), is selected from the group consisting of from about 2000 mPa·s to about 1 mPa·s, from about 1900 mPa·s to about 1 mPa·s, from about 1800 mPa·s to about 15 1 mPa·s, from about 1700 mPa·s to about 1 mPa·s, from about 1600 mPa·s to about 1 mPa·s, from about 1500 mPa·s to about 1 mPa·s, from about 1400 mPa·s to about 1 mPa·s, from about 1300 mPa·s to about 1 mPa·s, from about 1200 mPa·s to about 1 mPa·s, from about 1100 mPa·s to about 1 mPa·s, from about 1000 mPa·s to about 1 mPa·s, from about 900 mPa·s to about 1 mPa·s, from about 800 mPa·s to about 1 mPa·s, 20 from about 700 mPa·s to about 1 mPa·s, from about 600 mPa·s to about 1 mPa·s, from about 500 mPa·s to about 1 mPa·s, from about 400 mPa·s to about 1 mPa·s, from about 300 mPa·s to about 1 mPa·s, from about 200 mPa·s to about 1 mPa·s, from about 175 mPa·s to about 1 mPa·s, from about 150 mPa·s to about 1 mPa·s, from about 125 mPa·s to about 1 mPa·s, from about 100 mPa·s to about 1 mPa·s, from about 75 mPa·s to about 1 25 mPa·s, from about 50 mPa·s to about 1 mPa·s, from about 25 mPa·s to about 1 mPa·s, from about 15 mPa·s to about 1 mPa·s, from about 10 mPa·s to about 1 mPa·s, and from about 5 mPa·s to about 1 mPa·s.

33. The composition of claim 1, wherein the viscosity of the composition is 30 selected from the group consisting of less than about 1/200, less than about 1/100, less than about 1/50, less than about 1/25, and less than about 1/10 of the viscosity of a



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standard conventional non-nanoparticulate liquid dosage composition of the same active agent at about the same concentration per ml of active agent.

34. The composition of claim 1, wherein the viscosity of the composition is  
5 selected from the group consisting of less than about 5%, less than about 10%, less than about 15%, less than about 20%, less than about 25%, less than about 30%, less than about 35%, less than about 40%, less than about 45%, less than about 50%, less than about 55%, less than about 60%, less than about 65%, less than about 70%, less than about 75%, less than about 80%, less than about 85%, and less than about 90% of the  
10 viscosity of a standard conventional non-nanoparticulate liquid dosage composition of the same active agent at about the same concentration per ml of active agent.

35. The composition of claim 1, wherein the  $T_{max}$  of the active agent, when  
assayed in the plasma of a mammalian subject following administration, is less than the  
15  $T_{max}$  for a conventional, non-nanoparticulate form of the same active agent, administered at the same dosage.

36. The composition of claim 35, wherein the  $T_{max}$  is selected from the group  
consisting of not greater than about 90%, not greater than about 80%, not greater than  
20 about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, and not greater than about 10% of the  $T_{max}$ , exhibited by a non-nanoparticulate formulation of the same active agent, administered at the same dosage.

25 37. The composition of claim 1, wherein the  $C_{max}$  of the active agent, when assayed in the plasma of a mammalian subject following administration, is greater than the  $C_{max}$  for a conventional, non-nanoparticulate form of the same active agent, administered at the same dosage.

30 38. The composition of claim 37, wherein the  $C_{max}$  is selected from the group consisting of at least about 10%, at least about 20%, at least about 30%, at least about

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40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, and at least about 100% greater than the  $C_{max}$  exhibited by a non-nanoparticulate formulation of the same active agent, administered at the same dosage.

5           39.     The composition of claim 1, wherein the AUC of the active agent, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a conventional, non-nanoparticulate form of the same active agent, administered at the same dosage.

10           40.     The composition of claim 39, wherein the AUC is selected from the group consisting of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, and at least about 100% greater than the AUC exhibited by a non-nanoparticulate formulation of the same active agent, administered at the same dosage.

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          41.     The composition of claim 1 which does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

20           42.     The composition of claim 41, wherein the difference in absorption of the active agent composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

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          43.     The composition of claim 1, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, when administered to a human.

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44. The composition of claim 43, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for both  $C_{max}$  and AUC, when administered to a human.

5 45. The composition of claim 43, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for  $C_{max}$ , when administered to a human.

10 46. A method of making a stable nanoparticulate liquid dosage composition comprising contacting particles of at least one active agent with at least one surface stabilizer for a time and under conditions sufficient to provide a nanoparticulate active agent composition wherein:

(a) the active agent particles have an effective average particle size of less than about 2 microns; and

15 (b) at least one osmotically active crystal growth inhibitor is added to the composition either before, during, or after the active agent particle size reduction.

20 47. The method of claim 46, wherein said contacting comprising grinding.

48. The method of claim 47, wherein said grinding comprising wet grinding.

49. The method of claim 46, wherein said contacting comprises homogenizing.

25 50. The method of claim 46, wherein said contacting comprises:

(a) dissolving the particles of at least one active agent in a solvent;

(b) adding the resulting solution of the active agent to a solution comprising at least one surface stabilizer; and

30 (c) precipitating the solubilized active agent and at least one surface stabilizer by the addition thereto of a non-solvent.

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51. The method of claim 46, wherein the active agent particles form crystals upon storage or heating in the absence of the crystal growth inhibitor.

52. The method of claim 46, wherein the osmotically active crystal growth inhibitor is at least partially water-soluble and does not solubilize the nanoparticulate active agent.

53. The method of claim 52, wherein the osmotically active crystal growth inhibitor is selected from the group consisting of glycerol, propylene glycol, mannitol, sucrose, glucose, fructose, mannose, lactose, xylitol, sorbitol, trehalose, a polysaccharide, a mono-polysaccharide, a di-polysaccharides, a sugars, a sugar alcohol, sodium chloride, potassium chloride, magnesium chloride, and an ionic salt.

54. The method of claim 53, wherein the crystal growth inhibitor is glycerol.

55. The method of claim 53, where the crystal growth inhibitor is mannitol.

56. The method of claim 53, where the crystal growth inhibitor is sodium chloride.

57. The method of claim 46, wherein the amount of the crystal growth inhibitor present in the liquid dosage composition ranges from about 0.1% to about 95% concentration, by weight.

58. The method of claim 57, wherein the amount of the crystal growth inhibitor present in the liquid dosage composition ranges from about 0.5% to about 90% concentration, by weight.

59. The method of claim 46, wherein the effective average particle size of the nanoparticulate active agent particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600

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nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm,  
5 less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

60. The method of claim 46 or 59, wherein at least about 70%, about 90%, or about 95% of the active agent particles have a particle size less than the effective average  
10 particle size.

61. The method of claim 46, wherein the liquid media of the liquid dosage composition is selected from the group consisting of water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, and glycol.  
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62. The method of claim 46, wherein the at least one active agent is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the active agent and at least one surface stabilizer, not including  
20 other excipients.

63. The method of claim 46, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the active agent and at  
25 least one surface stabilizer, not including other excipients.

64. The method of claim 46, wherein the ratio of active agent to a polymeric surface modifier is selected from the group consisting of from about 20:1 to about 1:10,  
30 from about 10:1 to about 1:5, and from about 5:1 to about 1:1, by weight.

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65. The method of claim 46, comprising at least two surface stabilizers.

66. The method of claim 65, wherein the ratio of active agent to the second  
5 surface stabilizer is selected from the group consisting of from about 500:1 to about 5:1,  
from about 350:1 to about 10:1, and from about 100:1 to about 20:1, by weight.

67. The method of claim 46, wherein the surface stabilizer is selected from the  
group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a polymeric  
10 surface stabilizer, a nonionic surface stabilizer, and a zwitterionic surface stabilizer.

68. The method of claim 67, wherein the at least one surface stabilizer is  
selected from the group consisting of cetyl pyridinium chloride, gelatin, casein,  
phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid,  
15 benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol,  
cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers,  
polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters,  
polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates,  
colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose  
20 calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium,  
methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose,  
magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone,  
4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde,  
poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of  
25 sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures  
of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-  
methylglucamide; n-decyl  $\beta$ -D-glucopyranoside; n-decyl  $\beta$ -D-maltopyranoside; n-dodecyl  
 $\beta$ -D-glucopyranoside; n-dodecyl  $\beta$ -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-  
 $\beta$ -D-glucopyranoside; n-heptyl  $\beta$ -D-thioglucoside; n-hexyl  $\beta$ -D-glucopyranoside;  
30 nonanoyl-N-methylglucamide; n-noyl  $\beta$ -D-glucopyranoside; octanoyl-N-

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methylglucamide; n-octyl- $\beta$ -D-glucopyranoside; octyl  $\beta$ -D-thiogluco-pyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, and random copolymers of vinyl acetate and vinyl pyrrolidone.

- 5           69.     The method of claim 67, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, a phospholipid, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate,
- 10    hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride,
- 15    decyl dimethyl hydroxyethyl ammonium chloride bromide, C<sub>12-15</sub>dimethyl hydroxyethyl ammonium chloride, C<sub>12-15</sub>dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl
- 20    (ethenoxy)<sub>4</sub> ammonium chloride, lauryl dimethyl (ethenoxy)<sub>4</sub> ammonium bromide, N-alkyl (C<sub>12-18</sub>)dimethylbenzyl ammonium chloride, N-alkyl (C<sub>14-18</sub>)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C<sub>12-14</sub>) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-
- 25    dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkylamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C<sub>12-14</sub>) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl
- 30    benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C<sub>12</sub> trimethyl

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ammonium bromides, C<sub>15</sub> trimethyl ammonium bromides, C<sub>17</sub> trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyl dimethyl ammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, 5 dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearylalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™, ALKAQUAT™, alkyl pyridinium 10 salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

70. The method of claim 46, wherein the active agent is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a 15 semi-amorphous phase, and mixtures thereof.

71. The method of claim 46, wherein the one or more active agents have a solubility in water selected from the group consisting of less than about 30 mg/ml, less than about 20 mg/ml, less than about 10 mg/ml, and less than about 1 mg/ml, under 20 ambient conditions.

72. The method of claim 46, wherein the active agent comprises anti-inflammatory and analgesic properties.

25 73. The method of claim 46, wherein the at least one active agent is selected from the group consisting of COX-2 inhibitors, anticancer agents, NSAIDS, proteins, peptides, nutraceuticals, anti-obesity agents, corticosteroids, elastase inhibitors, analgesics, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, 30 anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic



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agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid  
5 regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, xanthines, acne medication, alpha-hydroxy formulations, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic  
10 bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, and respiratory illness therapies associated with acquired immune deficiency syndrome.

74. The method of claim 73, wherein the nutraceutical is selected from the  
15 group consisting of dietary supplements, vitamins, minerals, herbs, healing foods that have medical or pharmaceutical effects on the body, folic acid, fatty acids, fruit and vegetable extracts, vitamin supplements, mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants,  
20 flavonoid constituents of fruits, evening primrose oil, flax seeds, fish and marine animal oils, and probiotics.

75. The method of claim 46, wherein the active agent is selected from the group consisting of acyclovir, alprazolam, altretamine, amiloride, amiodarone,  
25 benztropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin, cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine, cyproheptadine, delavirdine, desmopressin, diltiazem, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine, felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole, loratadine, loxapine, mebendazole, mercaptopurine,  
30 milrinone lactate, minocycline, mitoxantrone, nelfinavir mesylate, nimodipine, norfloxacin, olanzapine, omeprazole, penciclovir, pimozide, tacolimus, quazepam,

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raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, sertraline, sildenafil, acetyl-sulfisoxazole, temazepam, thiabendazole, thioguanine, trandolapril, triamterene, trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenolate, atovaquone, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, 5 thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, and acetylsalicylate.

76. A method of treating a subject with a stable nanoparticulate liquid dosage composition comprising administering to the subject an effective amount of a composition comprising:

- 10 (a) particles of at least one active agent having an effective average particle size of less than about 2000 nm;
- (b) at least one surface stabilizer; and
- (c) at least one osmotically active crystal growth inhibitor.

15 77. The method of claim 76, wherein said subject is a human.

78. The method of claim 76, wherein the condition to be treated is selected from the group consisting of neoplastic diseases, breast cancer, endometrial cancer, uterine cancer, cervical cancer, prostate cancer, renal cancer, hormone replacement 20 therapy in post-menopausal women, endometriosis, hirsutism, dysmenorrhea, uterine bleeding, HIV wasting, cancer wasting, migraine headache, cachexia, anorexia, castration, oral contraception, motion sickness, emesis related to cytotoxic drugs, gastritis, ulcers, dyspepsia, gastroenteritis, including colitis and food poisoning, inflammatory bowel disease, Crohn's disease, migraine headaches, and any other condition which is 25 accompanied by the symptoms of nausea and vomiting.

79. The method of claim 76, wherein the condition to be treated is selected from the group consisting of pain, inflammation, arthritis, cancer, kidney disease, osteoporosis, Alzheimer's disease, and familial adenomatous polyposis.

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80. The method of claim 79, wherein the condition to be treated is selected from the group consisting of osteoarthritis, rheumatoid arthritis, juvenile arthritis, gout, ankylosing spondylitis, systemic lupus erythematosus, bursitis, tendinitis, myofascial pain, carpal tunnel syndrome, fibromyalgia syndrome, infectious arthritis, psoriatic arthritis, reiter's syndrome, and scleroderma.

81. The method of claim 76, wherein the active agent particles form crystals upon storage or heating in the absence of the crystal growth inhibitor.

82. The method of claim 76, wherein the osmotically active crystal growth inhibitor is at least partially water-soluble and does not solubilize the nanoparticulate active agent.

83. The method of claim 82, wherein the osmotically active crystal growth inhibitor is selected from the group consisting of glycerol, propylene glycol, mannitol, sucrose, glucose, fructose, mannose, lactose, xylitol, sorbitol, trehalose, a polysaccharide, a mono-polysaccharide, a di-polysaccharides, a sugars, a sugar alcohol, sodium chloride, potassium chloride, magnesium chloride, and an ionic salt.

84. The method of claim 83, wherein the crystal growth inhibitor is glycerol.

85. The method of claim 83, where the crystal growth inhibitor is mannitol.

86. The method of claim 83, where the crystal growth inhibitor is sodium chloride.

87. The method of claim 76, wherein the amount of the crystal growth inhibitor present in the liquid dosage composition ranges from about 0.1% to about 95% concentration, by weight.

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88. The method of claim 76, wherein the amount of the crystal growth inhibitor present in the liquid dosage composition ranges from about 0.5% to about 90% concentration, by weight.

5 89. The method of claim 76, wherein the effective average particle size of the nanoparticulate active agent particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900  
10 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

15 90. The method of claim 76 or 89, wherein at least about 70%, about 90%, or about 95% of the active agent particles have a particle size less than the effective average particle size.

20 91. The method of claim 76, wherein the amount of the active agent per ml is equal to or greater than the amount of the active agent per ml of a standard conventional non-nanoparticulate liquid dosage composition of the same active agent.

25 92. The method of claim 76, wherein the liquid media of the liquid dosage composition is selected from the group consisting of water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, and glycol.

30 93. The method of claim 76, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

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94. The method of claim 76 formulated into a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

95. The method of claim 76, wherein the at least one active agent is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the active agent and at least one surface stabilizer, not including other excipients.

96. The method of claim 76, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the active agent and at least one surface stabilizer, not including other excipients.

97. The method of claim 76, wherein the ratio of active agent to a polymeric surface modifier is selected from the group consisting of from about 20:1 to about 1:10, from about 10:1 to about 1:5, and from about 5:1 to about 1:1, by weight.

98. The method of claim 76, comprising at least two surface stabilizers.

99. The method of claim 98, wherein the ratio of active agent to the second surface stabilizer is selected from the group consisting of from about 500:1 to about 5:1, from about 350:1 to about 10:1, and from about 100:1 to about 20:1, by weight.

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100. The method of claim 76, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

101. The method of claim 76, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a polymeric surface stabilizer, a nonionic surface stabilizer, and a zwitterionic surface stabilizer.

102. The method of claim 101, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl  $\beta$ -D-glucopyranoside; n-decyl  $\beta$ -D-maltopyranoside; n-dodecyl  $\beta$ -D-glucopyranoside; n-dodecyl  $\beta$ -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl  $\beta$ -D-glucopyranoside; n-heptyl  $\beta$ -D-thiogluconoside; n-hexyl  $\beta$ -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl  $\beta$ -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- $\beta$ -D-glucopyranoside; octyl  $\beta$ -D-thiogluconoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, and random copolymers of vinyl acetate and vinyl pyrrolidone.

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103. The method of claim 101, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, a phospholipid, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, 5 hexadecyltrimethyl ammonium bromide, phosphonium compounds, quaternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, 10 decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C<sub>12-15</sub>dimethyl hydroxyethyl ammonium chloride, C<sub>12-15</sub>dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl 15 ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)<sub>4</sub> ammonium chloride, lauryl dimethyl (ethenoxy)<sub>4</sub> ammonium bromide, N-alkyl (C<sub>12-18</sub>)dimethylbenzyl ammonium chloride, N-alkyl (C<sub>14-18</sub>)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C<sub>12-14</sub>) dimethyl 1-naphthylmethyl 20 ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C<sub>12-14</sub>) dimethyl 1- 25 naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C<sub>12</sub> trimethyl ammonium bromides, C<sub>15</sub> trimethyl ammonium bromides, C<sub>17</sub> trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium 30 chloride (DADMAC), dimethyl ammonium chlorides, alkyl dimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide,

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dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl triocrylammonium chloride, POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearylalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™, ALKAQUAT™, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

104. The method of claim 76, wherein the active agent is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, and mixtures thereof.

105. The method of claim 76, wherein the one or more active agents have a solubility in water selected from the group consisting of less than about 30 mg/ml, less than about 20 mg/ml, less than about 10 mg/ml, and less than about 1 mg/ml, under ambient conditions.

106. The method of claim 76, wherein the active agent comprises anti-inflammatory and analgesic properties.

107. The method of claim 76, wherein the at least one active agent is selected from the group consisting of COX-2 inhibitors, anticancer agents, NSAIDs, proteins, peptides, nutraceuticals, anti-obesity agents, corticosteroids, elastase inhibitors, analgesics, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid



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regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, xanthines, acne medication, alpha-hydroxy formulations, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, and respiratory illness therapies associated with acquired immune deficiency syndrome.

108. The method of claim 107, wherein the nutraceutical is selected from the group consisting of dietary supplements, vitamins, minerals, herbs, healing foods that have medical or pharmaceutical effects on the body, folic acid, fatty acids, fruit and vegetable extracts, vitamin supplements, mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish and marine animal oils, and probiotics.

109. The method of claim 76, wherein the active agent is selected from the group consisting of acyclovir, alprazolam, altretamine, amiloride, amiodarone, benztropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin, cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine, cyproheptadine, delavirdine, desmopressin, diltiazem, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine, felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole, loratadine, loxapine, mebendazole, mercaptopurine, milrinone lactate, minocycline, mitoxantrone, nelfinavir mesylate, nimodipine, norfloxacin, olanzapine, omeprazole, penciclovir, pimozone, tacolimus, quazepam, raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, sertraline, sildenafil, acetyl-sulfisoxazole, temazepam, thiabendazole, thioguanine, trandolapril, triamterene, trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenolate,

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atovaquone, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, and acetylsalicylate.

110. The method of claim 76, wherein the viscosity of the composition, at a shear rate of 0.1 (1/s), is selected from the group consisting of from about 2000 mPa·s to about 1 mPa·s, from about 1900 mPa·s to about 1 mPa·s, from about 1800 mPa·s to about 1 mPa·s, from about 1700 mPa·s to about 1 mPa·s, from about 1600 mPa·s to about 1 mPa·s, from about 1500 mPa·s to about 1 mPa·s, from about 1400 mPa·s to about 1 mPa·s, from about 1300 mPa·s to about 1 mPa·s, from about 1200 mPa·s to about 1 mPa·s, from about 1100 mPa·s to about 1 mPa·s, from about 1000 mPa·s to about 1 mPa·s, from about 900 mPa·s to about 1 mPa·s, from about 800 mPa·s to about 1 mPa·s, from about 700 mPa·s to about 1 mPa·s, from about 600 mPa·s to about 1 mPa·s, from about 500 mPa·s to about 1 mPa·s, from about 400 mPa·s to about 1 mPa·s, from about 300 mPa·s to about 1 mPa·s, from about 200 mPa·s to about 1 mPa·s, from about 175 mPa·s to about 1 mPa·s, from about 150 mPa·s to about 1 mPa·s, from about 125 mPa·s to about 1 mPa·s, from about 100 mPa·s to about 1 mPa·s, from about 75 mPa·s to about 1 mPa·s, from about 50 mPa·s to about 1 mPa·s, from about 25 mPa·s to about 1 mPa·s, from about 15 mPa·s to about 1 mPa·s, from about 10 mPa·s to about 1 mPa·s, and from about 5 mPa·s to about 1 mPa·s.

111. The method of claim 76, wherein the viscosity of the composition is selected from the group consisting of less than about 1/200, less than about 1/100, less than about 1/50, less than about 1/25, and less than about 1/10 of the viscosity of a standard conventional non-nanoparticulate liquid dosage composition of the same active agent at about the same concentration per ml of active agent.

112. The method of claim 76, wherein the viscosity of the composition is selected from the group consisting of less than about 5%, less than about 10%, less than about 15%, less than about 20%, less than about 25%, less than about 30%, less than about 35%, less than about 40%, less than about 45%, less than about 50%, less than about 55%, less than about 60%, less than about 65%, less than about 70%, less than

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about 75%, less than about 80%, less than about 85%, and less than about 90% of the viscosity of a standard conventional non-nanoparticulate liquid dosage composition of the same active agent at about the same concentration per ml of active agent.

5           113. The method of claim 76, wherein the  $T_{max}$  of the active agent, when assayed in the plasma of a mammalian subject following administration, is less than the  $T_{max}$  for a conventional, non-nanoparticulate form of the same active agent, administered at the same dosage.

10           114. The method of claim 113, wherein the  $T_{max}$  is selected from the group consisting of not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, and not greater than about 10% of the  $T_{max}$ , exhibited by a non-nanoparticulate  
15 formulation of the same active agent, administered at the same dosage.

          115. The method of claim 76, wherein the  $C_{max}$  of the active agent, when assayed in the plasma of a mammalian subject following administration, is greater than the  $C_{max}$  for a conventional, non-nanoparticulate form of the same active agent,  
20 administered at the same dosage.

          116. The method of claim 115, wherein the  $C_{max}$  is selected from the group consisting of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at  
25 least about 90%, and at least about 100% greater than the  $C_{max}$  exhibited by a non-nanoparticulate formulation of the same active agent, administered at the same dosage.

          117. The method of claim 76, wherein the AUC of the active agent, when assayed in the plasma of a mammalian subject following administration, is greater than  
30 the AUC for a conventional, non-nanoparticulate form of the same active agent, administered at the same dosage.

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118. The method of claim 117, wherein the AUC is selected from the group consisting of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, and at least about 100% greater than the AUC exhibited by a non-nanoparticulate formulation of the same active agent, administered at the same dosage.

119. The method of claim 76 which does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

120. The method of claim 119, wherein the difference in absorption of the active agent composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

121. The method of claim 76, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, when administered to a human.

122. The method of claim 121, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for both  $C_{max}$  and AUC, when administered to a human.

123. The method of claim 121, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for  $C_{max}$ , when administered to a human.